



# Detection of Transient Increase of Cerebral Blood Flow and Reversible Neuronal Dysfunction by Iodine-123-Iomazenil Single Photon Emission Computed Tomography After Cerebral Hyperperfusion Syndrome After Revascularization Surgery for Moyamoya Disease

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## Key words

- Cerebral hyperperfusion
- IMZ SPECT
- Moyamoya disease
- Neuronal damage

## Abbreviations and Acronyms

- CBF:** Cerebral blood flow  
**CBZ:** Central benzodiazepine  
**CMRO<sub>2</sub>:** Cerebral metabolic oxygen rates  
**<sup>123</sup>I-IMP:** <sup>123</sup>I-N-isopropyl-p-iodoamphetamine  
**<sup>123</sup>I-IMZ:** <sup>123</sup>I-iomazenil  
**MCA:** Middle cerebral artery  
**MR:** Magnetic resonance  
**PET:** Positron emission tomography  
**SPECT:** Single photon emission computed tomography  
**STA:** Superficial temporal artery

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## INTRODUCTION

<sup>123</sup>I-iomazenil (<sup>123</sup>I-IMZ) is a specific radioligand for central benzodiazepine (CBZ) receptors expressing sufficiently in the membrane of neurons, and single photon emission computed tomography (SPECT) using this ligand has been used to reveal pathologic lesions such as epilepsy, stroke, and traumatic brain injury.<sup>1-4</sup> <sup>123</sup>I-IMZ SPECT study is conducted in 2 phases: 1) images obtained within 30 minutes after administration of <sup>123</sup>I-IMZ (early images) correlate with the distribution of cerebral blood flow (CBF),<sup>5</sup> and 2) those at 180

■ **BACKGROUND:** Early and late images of single photon emission computed tomography (SPECT) using <sup>123</sup>I-iomazenil (<sup>123</sup>I-IMZ) can demonstrate cerebral blood flow and cortical neuronal viability. Hyperperfusion syndrome is one of the serious complications after revascularization surgery for moyamoya disease; therefore, the real-time observation of the hemodynamics and neuronal viability is important for the treatment after the revascularization. Here we report, a case of moyamoya disease where <sup>123</sup>I-IMZ SPECT had a significant efficacy to delineate the hemodynamics and transient neuronal dysfunction in hyperperfusion state after revascularization.

■ **CASE DESCRIPTION:** A 47-year-old woman presented with motor aphasia 3 days after superficial temporal artery—middle cerebral artery anastomosis with indirect revascularization. Magnetic resonance imaging (MRI) on the same day showed no new ischemic changes but high intensities along the left frontal sulci observed on fluid-attenuated inversion recovery images, and <sup>123</sup>I-IMZ SPECT demonstrated the increased uptake on the early images and the decreased uptake on the late images around the anastomosis site. The patient was completely recovered 1 month after surgery, and abnormal changes on MRI and <sup>123</sup>I-IMZ SPECT returned to normal along with the symptom withdrawal.

■ **CONCLUSIONS:** These findings indicate that <sup>123</sup>I-IMZ SPECT could be the index for the treatment of revascularization for obstructive vascular diseases such as moyamoya disease.

minutes after the tracer administration (late images) are in proportion to the density of the CBZ receptors representing brain neural density.<sup>2,6,7</sup> Furthermore, it has been indicated that late images could demonstrate a reversible neuronal damage or dysfunction.<sup>8,9</sup> Therefore, early and late images of <sup>123</sup>I-IMZ SPECT have different roles to measure hemodynamics, and cortical neuronal function and viability, respectively.

Cerebral hyperperfusion is the hemodynamic state of a significant increase in CBF with the disruption of autoregulation, and has been reported to occur in 15%–38% of patients with adult moyamoya disease after superficial temporal artery (STA)—middle cerebral artery (MCA)

anastomosis.<sup>10,11</sup> Symptoms are reversible in most patients, but rarely severe and life-threatening. Therefore, accurate and prompt demonstration of the hemodynamic state and the neuronal dysfunction is critical to adequate management.

CBF cannot be examined in the ordinary clinical practice without using special diagnostic equipment such as computed tomography and magnetic resonance (MR) perfusion imaging, SPECT using <sup>123</sup>I-N-isopropyl-p-iodoamphetamine (<sup>123</sup>I-IMP) and <sup>99m</sup>Tc-ethyl cysteinate dimer, and positron emission tomography (PET) scan using <sup>15</sup>O with a steady-state method.<sup>12,13</sup> Similarly, neuronal activity can be only measured as cerebral metabolic rate of oxygen using <sup>15</sup>O-PET.<sup>14</sup> Therefore, demonstration of the

causal brain lesion for a temporary neurologic symptom because of hyperperfusion without abnormal findings on ordinary neuroradiologic imaging is difficult.

Here, we report the efficacy of  $^{123}\text{I}$ -IMZ SPECT to reveal the hyperperfusion state after revascularization by demonstrating hemodynamic state on the early image and temporary neuronal dysfunction on the late image in moyamoya disease.

## CLINICAL PRESENTATION

A 47-year-old woman was referred to our hospital with speech disturbance for 2 weeks. On admission, her spontaneous speech was fluent, but word-finding difficulties were noticed. MR imaging demonstrated subacute hemorrhage in the left subcortical temporal lobe (Figure 1A and B). Digital subtraction angiography revealed stenotic changes around the terminal portions of the bilateral internal carotid arteries with abnormal proliferation of moyamoya vessels, and she was diagnosed with moyamoya disease (Figure 1C and D). Preoperative MR imaging revealed no abnormal lesion other than a scar resulting from intracerebral hemorrhage (Figure 2A), and MR angiography showed severe stenoses of the bilateral internal carotid arteries at the terminal portions (Figure 2B).  $^{123}\text{I}$ -IMP SPECT showed decrease of CBF in the bilateral cerebral hemispheres (Figure 2C). On the early and late images of  $^{123}\text{I}$ -IMZ SPECT before treatment, there were no evident lateralities (Figure 2D and E).

For the prevention of a future rebleeding, she underwent STA-MCA double anastomoses with indirect revascularization surgery in the left hemisphere at 3 months after the onset of intracranial hemorrhage. The recipient arteries at the M4 segment of the left frontal and temporal lobes were anastomosed to the parietal and frontal branches of the left STA, respectively, then, encephalo-duro-myo-synangiosis was also performed in the left fronto-temporal area. We controlled systolic blood pressure from 100 to 140 mm Hg after the operation.

She presented with motor aphasia on day 3. MR imaging showed no new ischemic changes, but high intensities along the left

frontal sulci were observed on fluid-attenuated inversion recovery images (Figure 2F). The patency of STA-MCA anastomosis was confirmed by MR angiography (Figure 2G). The images of  $^{123}\text{I}$ -IMP SPECT revealed marked increase of the CBF around the anastomosis site of the frontal lobe (Figure 2H). The uptake in the responsible lesion for motor aphasia was increased on the early images of  $^{123}\text{I}$ -IMZ SPECT corresponding to those of  $^{123}\text{I}$ -IMP SPECT (Figure 2I), whereas the uptake on the late images was remarkably decreased (Figure 2J). We diagnosed this as hyperperfusion syndrome, and the patient's systolic blood pressure was more strictly controlled from 100 to 120 mm Hg with continuous administration of a calcium channel blocker. The symptom gradually resolved by blood pressure control, and the patient was completely recovered 1 month after surgery. High intensities on fluid-attenuated inversion recovery images along the left frontal sulci disappeared (Figure 2K). MR angiography showed the patency of the bypass (Figure 2L).  $^{123}\text{I}$ -IMP SPECT demonstrated normalization of hyperperfusion (Figure 2M). Abnormal findings on both early and late images of  $^{123}\text{I}$ -IMZ SPECT were also normalized along with symptom withdrawal (Figure 2N and O).

## Consent

The second author of this paper has obtained patient consent for anonymized publication of the case.

## DISCUSSION

This case report demonstrated the effectiveness of  $^{123}\text{I}$ -IMZ SPECT in detecting transient increase of CBF and reversible vulnerability of neurons in cerebral hyperperfusion syndrome after revascularization surgery for moyamoya disease.

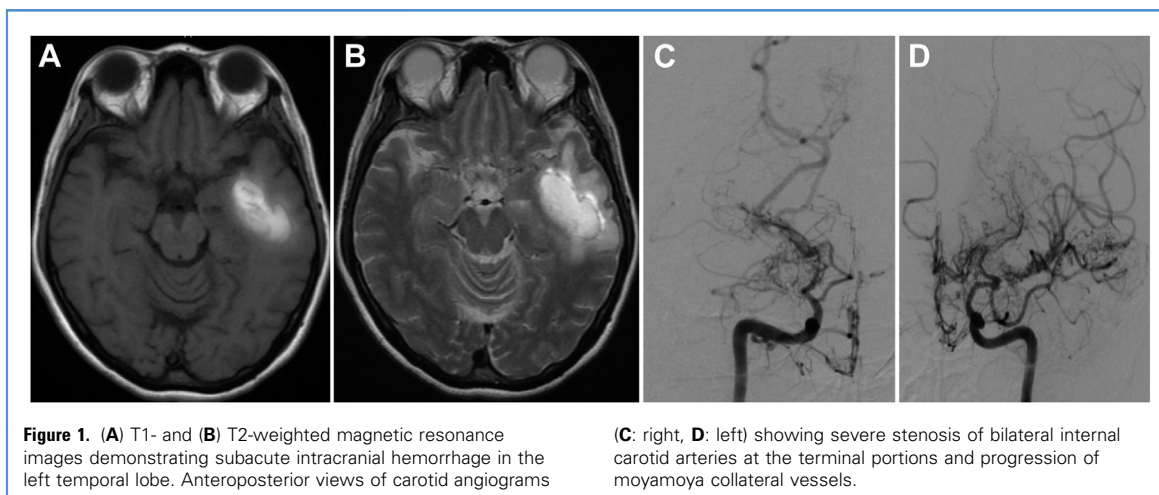
$^{123}\text{I}$ -IMP SPECT with autoradiographic method and  $^{15}\text{O}$ -PET remain the criterion standard for the accurate diagnosis of postoperative hyperperfusion. Early images of  $^{123}\text{I}$ -IMZ SPECT were reported to correlate with CBF images on  $^{15}\text{O}$ -PET,<sup>5</sup> and the early images of the present case showed increased uptake, corresponding to the findings of  $^{123}\text{I}$ -IMP SPECT. Therefore,  $^{123}\text{I}$ -IMZ SPECT early images can be an alternative modality for the diagnosis of cerebral hyperperfusion.

However, CBF images of  $^{123}\text{I}$ -IMZ SPECT are not quantitative, which is a disadvantage compared with  $^{123}\text{I}$ -IMP SPECT, the current criterion standard for CBF measurement. Although the dose is not high,  $^{123}\text{I}$ -IMZ SPECT has a disadvantage that patients are exposed to approximately 5 mSv of radiation,<sup>15</sup> which is almost equivalent to cranial CT scan (3 mSv).

On the other hand, in recent years, MR perfusion has been used to detect postoperative hyperperfusion state. Cerebral blood volume can be measured by perfusion MR imaging with gadolinium-based contrast agents, and it has been applied to detect hyperperfusion state not only after carotid revascularization,<sup>16</sup> but also after STA-MCA anastomosis in moyamoya disease.<sup>17</sup> In addition, intracranial hemodynamics have been recently examined by arterial spin labeling perfusion without contrast agents, and its usefulness in detecting hyperperfusion state in moyamoya disease has been reported.<sup>18,19</sup> Accuracy of diagnosis may be inferior to SPECT, but MR perfusion has an advantage of avoiding radiation exposure, and this imaging technique should be developed further in the near future.

Late  $^{123}\text{I}$ -IMZ SPECT images demonstrated postoperative cortical neuronal loss in hyperperfusion after carotid endarterectomy, and postoperative cognitive impairment was significantly associated with the decrease of uptake.<sup>20</sup> Recently, effectiveness was also demonstrated in hyperperfusion after revascularization for carotid stenosis and moyamoya disease,<sup>21,22</sup> which is consistent with this report.

Although reduced uptake on the late  $^{123}\text{I}$ -IMZ SPECT images is considered as irreversible, recent reports have shown that the late images of this radioligand could also demonstrate a reversible neuronal damage or dysfunction. The reduced uptake after head trauma recovered as the neurologic function improved,<sup>8</sup> and the reduction of uptake around the tumor recovered after the surgical removal along with the improvement of cognitive function.<sup>9</sup> Consistent with these reports, the reduction of the uptake on late images of the present case recovered along with the disappearance of the symptom. It is suggested that  $^{123}\text{I}$ -IMZ SPECT late images have the



**Figure 1.** (A) T1- and (B) T2-weighted magnetic resonance images demonstrating subacute intracranial hemorrhage in the left temporal lobe. Anteroposterior views of carotid angiograms

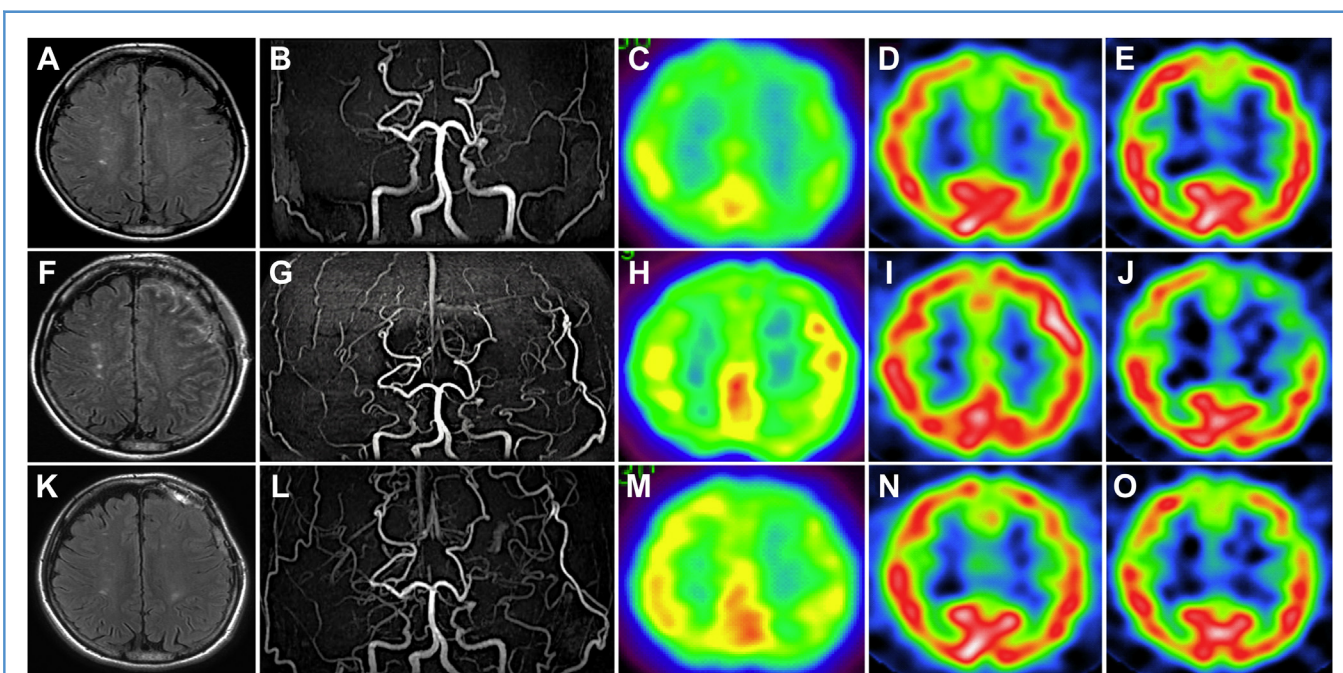
(C: right, D: left) showing severe stenosis of bilateral internal carotid arteries at the terminal portions and progression of moyamoya collateral vessels.

potential to detect reversible viability of neurons.

Although the detailed mechanism for the reduction of CBZ receptors binding affinity during the acute phase of brain injury remains obscure, one of the speculated mechanisms is the reduction of

cerebral metabolic oxygen rates ( $CMRO_2$ ). The relationship between the binding affinity of CBZ receptors and cerebral metabolism was investigated in patients with traumatic brain injury using flumazenil PET, and all the areas of decreased flumazenil uptake showed low  $CMRO_2$ .<sup>23</sup>

Shimada et al.<sup>22</sup> recently reported that crossed cerebellar hypoperfusion was observed on  $^{123}I$ -IMP SPECT, indicating the reduction of metabolism in the contralateral cerebral hemisphere, in company with the decreased uptake on  $^{123}I$ -IMZ SPECT late images during



**Figure 2.** (A–E) Preoperative images. Fluid-attenuated inversion recovery (FLAIR) (A). Magnetic resonance (MR) angiography (B).  $^{123}I$ -N-isopropyl-p-iodoamphetamine ( $^{123}I$ -IMP) single photon emission computed tomography (SPECT) revealing decrease of cerebral blood flow (CBF) in the bilateral cerebral hemispheres (C).  $^{123}I$ -iomazenil ( $^{123}I$ -IMZ) SPECT (D: early, E: delay) showing no lateralities. (F–J) Images during the period of hyperperfusion syndrome. FLAIR images showing high intensities along the left frontal sulci (F). MR angiography revealing the patency of superficial temporal artery–middle cerebral artery anastomosis (G).

$^{123}I$ -IMP SPECT revealing increased rest CBF around the anastomosis site of the left frontal lobe (H) in accordance with the increased uptake on the early images of  $^{123}I$ -IMZ SPECT (I). Late images of  $^{123}I$ -IMZ SPECT showing the remarkable decrease of the uptake in the lesion (J). (K–O) Images 1 month after the surgery. Fluid-attenuated inversion recovery images showing no additional abnormal changes (K). MR angiography revealing the patency of bypass (L).  $^{123}I$ -IMP SPECT demonstrating disappearance of hyperperfusion at the left frontal lobe (M). Both early (N) and late (O) images of  $^{123}I$ -IMZ SPECT showing improvement of abnormal findings.

hyperperfusion after revascularization surgery of moyamoya disease. Then, they suggested that the reduction of cerebral metabolism would downregulate cortical neurotransmitter receptors including CBZ. However, the reduction of CBZ receptors binding affinity in the present case cannot be explained by this mechanism because crossed cerebellar diaschisis was not observed in the present case (data not shown). Moreover, a previous study reported that CMRO<sub>2</sub> in patients with hyperperfusion after revascularization of moyamoya disease was not reduced.<sup>24</sup> Therefore, further investigation of the CBZ receptors binding affinity and cerebral metabolism is necessary to clarify the mechanism and the discrepancy of these findings.

Finally, <sup>123</sup>I-IMZ SPECT can indicate information not only about CBF, but also neuronal viability. Therefore, this imaging modality would be useful for the understanding of complex pathologic conditions in patients with moyamoya disease after revascularization, which would enable us to manage patients appropriately and promptly. In addition, there is a possibility that <sup>123</sup>I-IMZ SPECT would predict the prognosis of patients after hyperperfusion syndrome because it can disclose the reversibility of neurologic dysfunction. Further studies should be conducted to prove these issues.

## CONCLUSIONS

<sup>123</sup>I-IMZ SPECT findings of the present case suggest its effectiveness in detecting transient increase of CBF and reversible vulnerability of neurons simultaneously.

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